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(54) MEASURING BLOOD
CLOTTING TIME

(57) A blood clotting end point detector which includes means for monitoring an electrical signal representing the value A of one or more optical properties of a blood plasma sample to which a coagulating agent has been added, means for deriving the first and the second differentials with respect to time of the value A, and takes as the end point the movement when the second differential becomes positive, may be inaccurate because with dilute and abnormal plasmas clotting is intermittent and non-uniform. Hence the present invention includes means for detecting the moment Ta when the second differential becomes positive as well as means for detecting the subsequent movement T_b when it changes from positive to negative, means for deriving the difference (R) between the tangent to the curve A at the moment Ta and the curve A, and means for determining whether the difference (R) or the integral, with respect to time from moment Ta to moment Tb, of the difference (R) exceeds a predetermined threshold value, in which case moment Tb is taken as the true clotting end point.
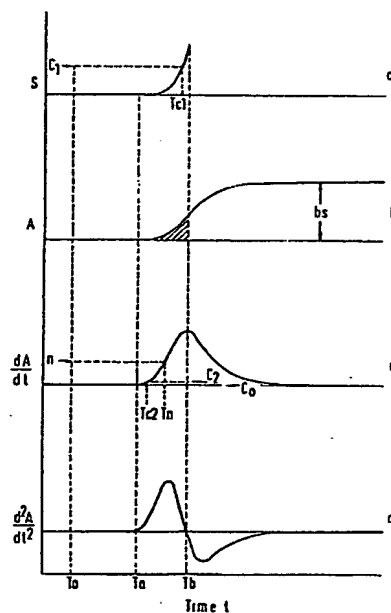
FIG.2.

FIG.1.

FIG.2.

FIG.3.

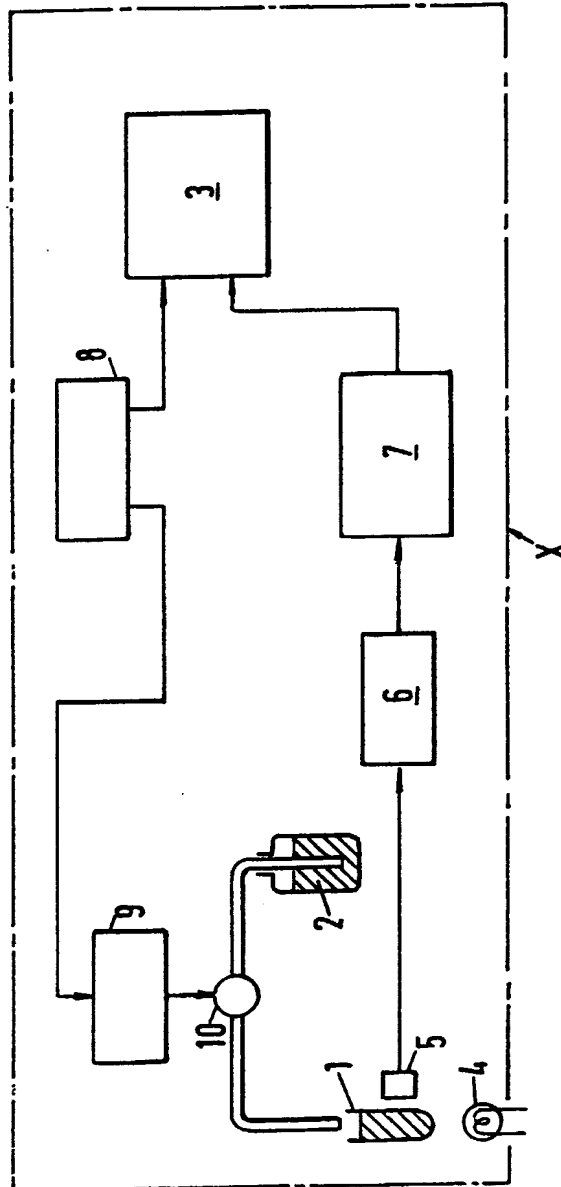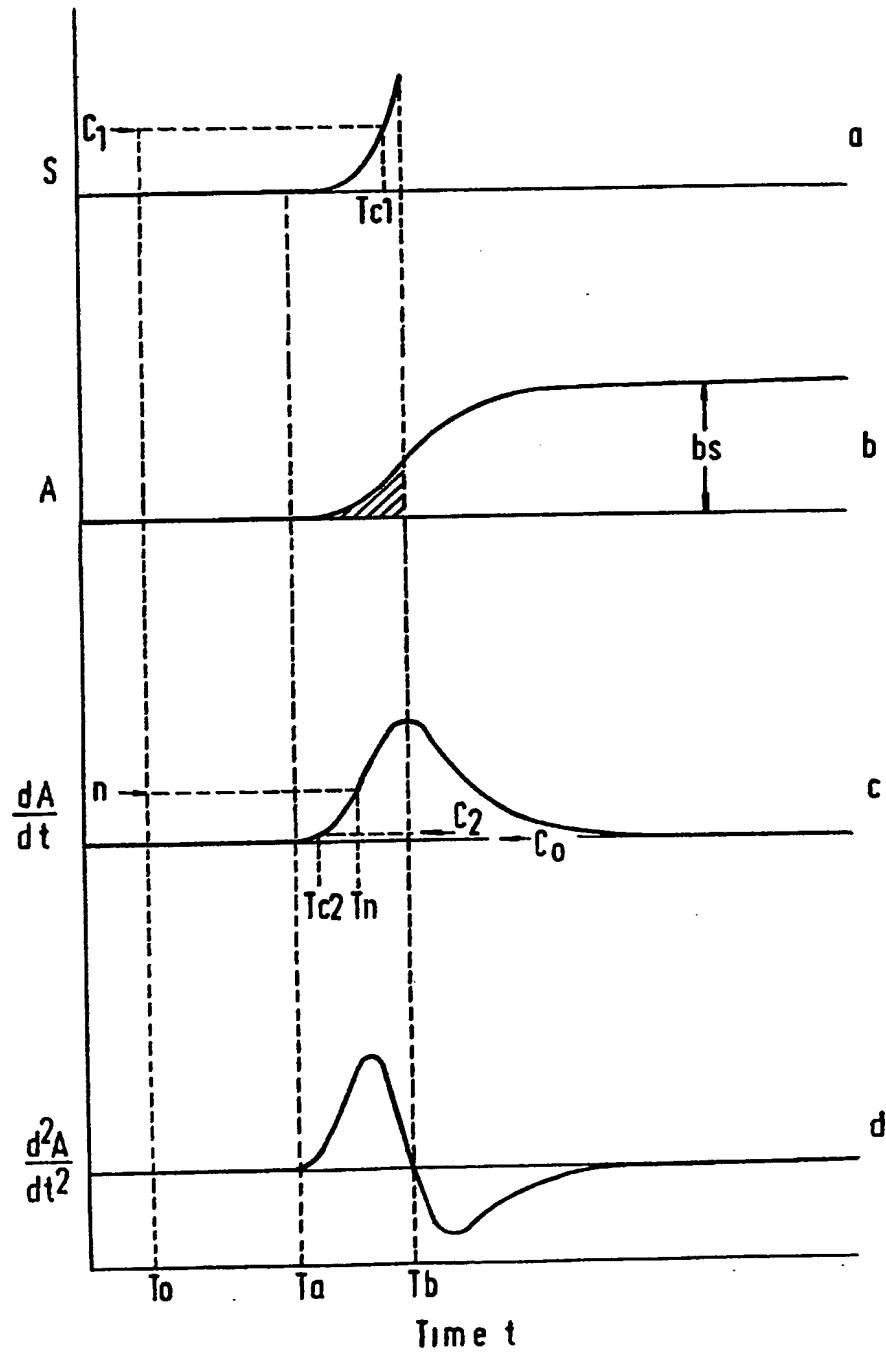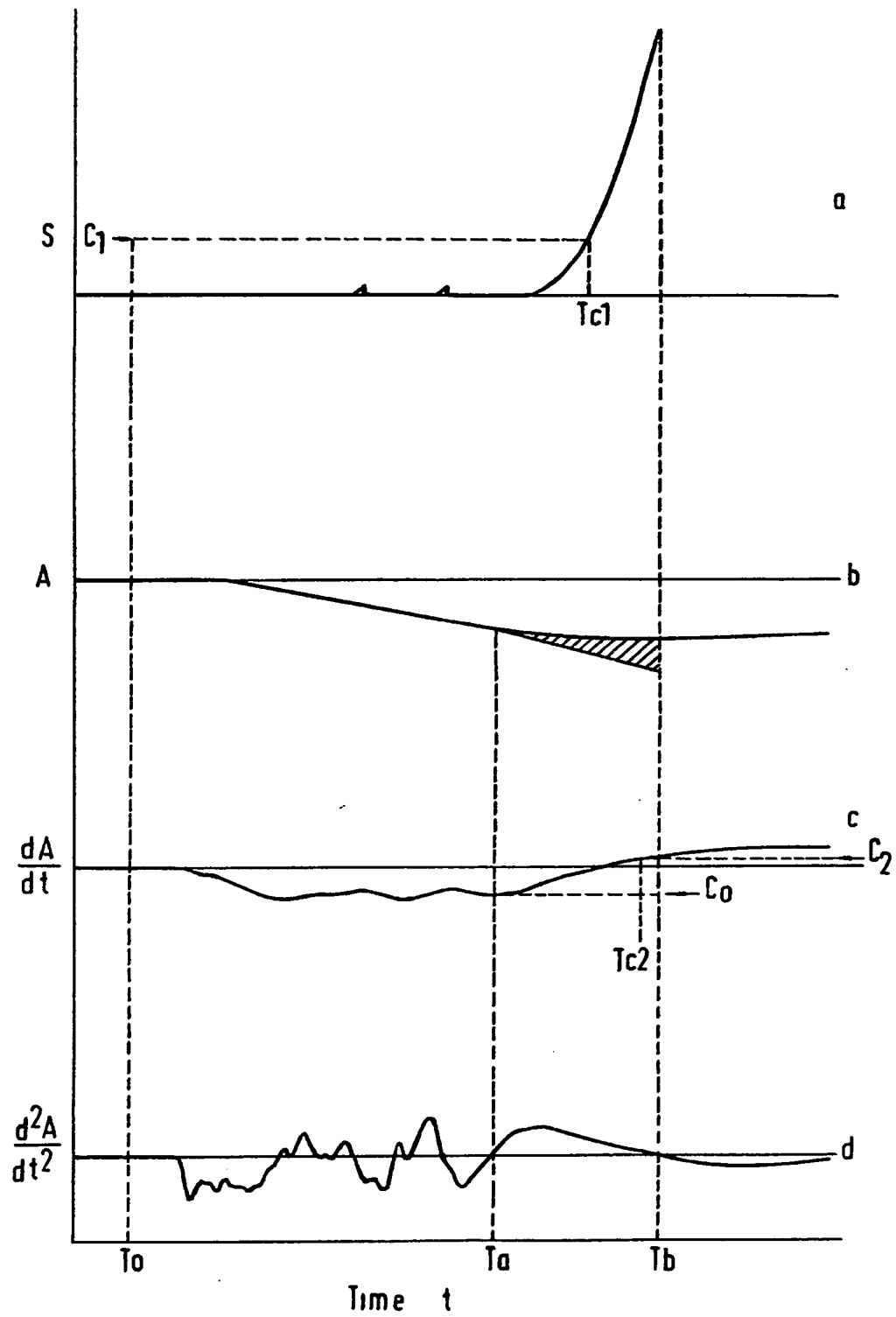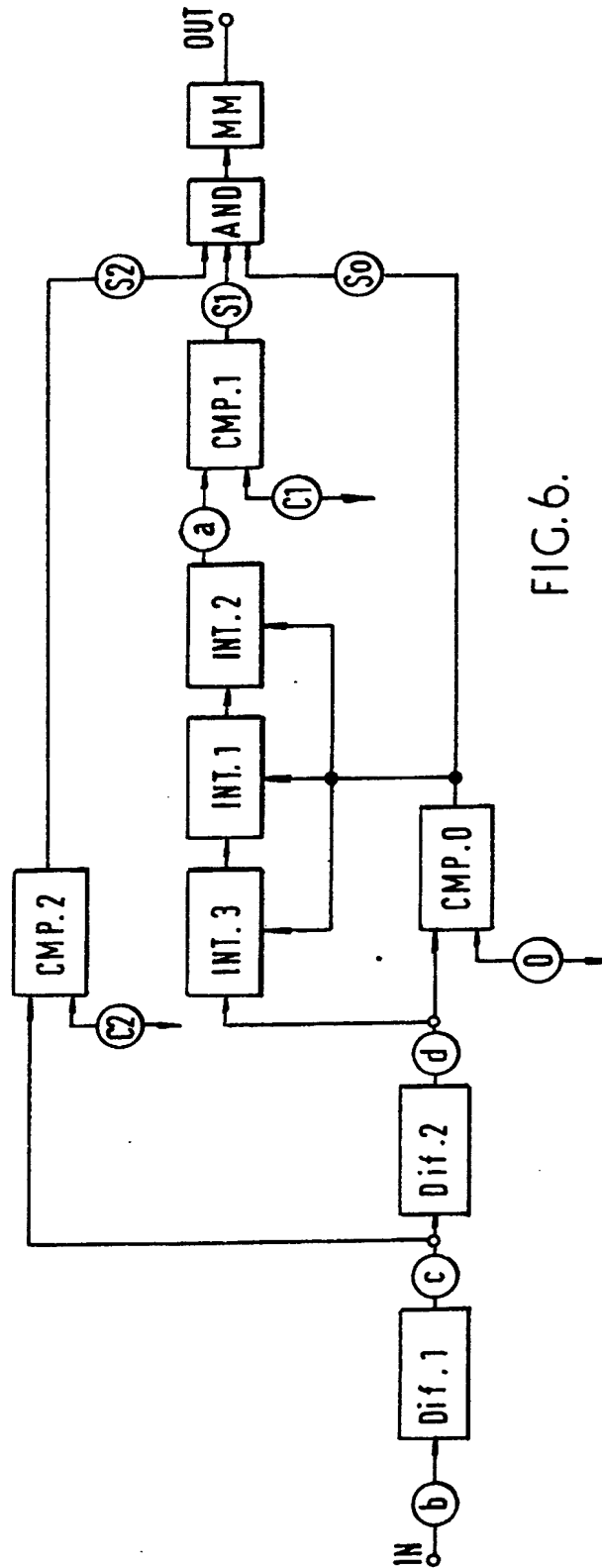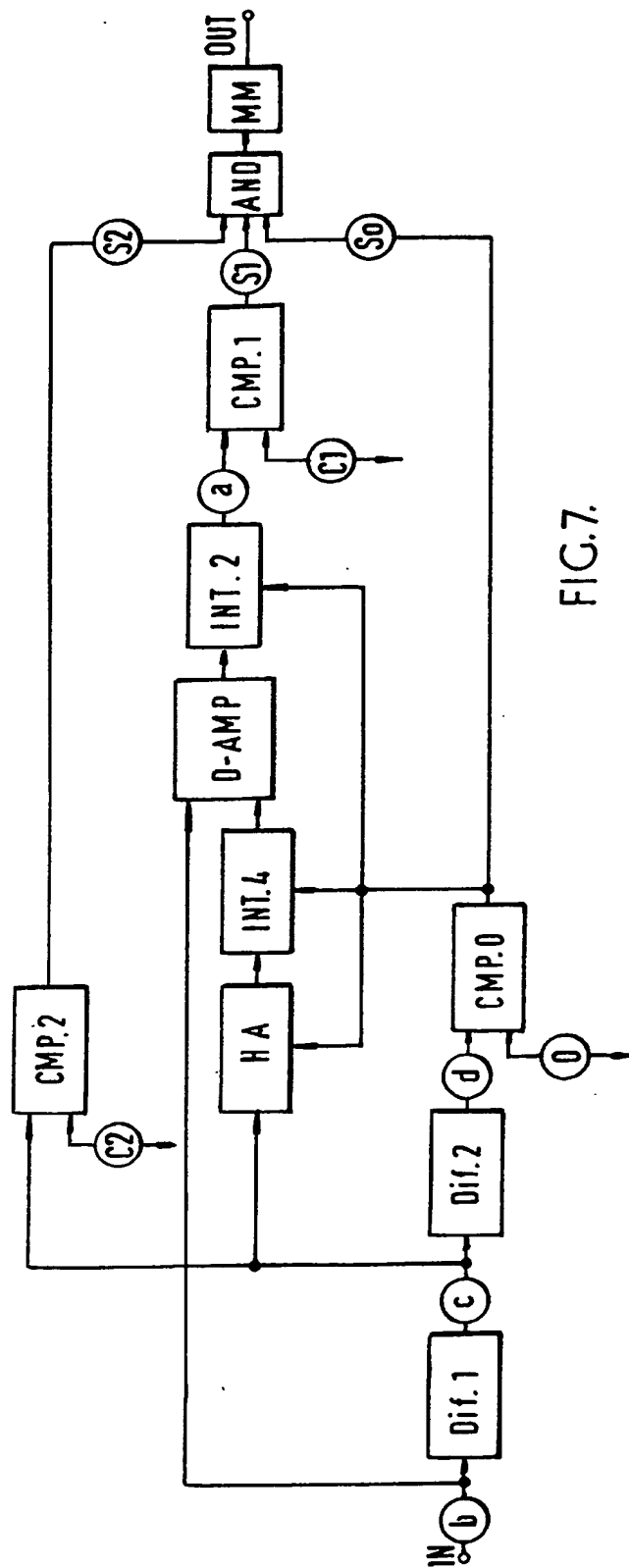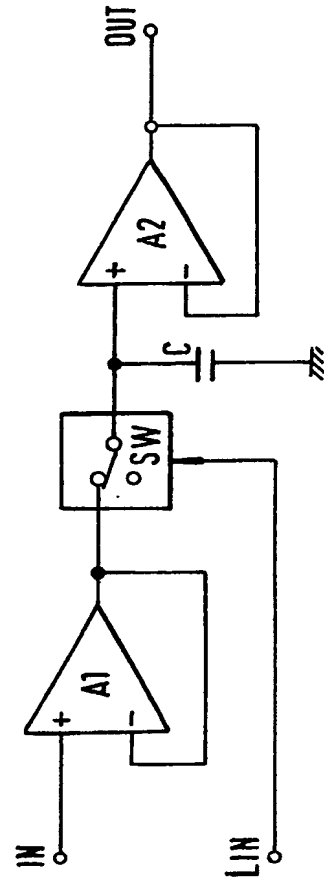FIG.4.

FIG.5.

FIG.6.

FIG.7.

FIG.8.

SPECIFICATION

METHOD OF MEASURING BLOOD CLOTTING TIME

In the present invention, an improvement is
5 made to the clotting end point detector of a
known blood clotting time measuring device to
facilitate the accurate and consistent detection of
the clotting end point to provide a reliable
measurement of the blood clotting time.
10   Measuring blood coagulation or clotting time is
necessary for caring for medical patients with
tendencies to bleed and for controlling anti-
coagulant therapy for thrombotic diseases.
Representative techniques employed are
15 Prothrombin Time measurement (PT) for
checking the extrinsic coagulation system,
Activated Partial Thromboplastine Time
measurement (APTT) for the intrinsic system and
Partial Thromboplastine Time measurement
20 (PTT).
In the above mentioned PT technique a reagent
(such as Simplastin manufactured by Warner-
Lambert) is added to a plasma sample separated
from the blood. An optical property of the sample
25 is then monitored, such as (1) absorbence, (2)
transmittance or optical attenuation ratio, (3)
intensity or its logarithm of the light scattered by
the sample, (4) refractive index, or (5) the sum or
difference of the above going (1), (2), (3) and (4).
30 Hereinafter, the instantaneous value of the
monitored optical property or properties will be
designated as A. The moment when the detected
value of A changes radically is taken as the point
where clotting ends, and the time interval from
35 when the reagent is added to when clotting ends is
taken as the prothrombin time or PT.
In the APTT technique a reagent (such as
Platelin-plus-activator manufactured by Warner-
Lambert) is added to a plasma sample, which is
40 activated at 37°C for a length of time specified for
the reagent (such as for 5 minutes). Then a
coagulant agent (such as a solution of calcium
chloride) is added. As in the case of the PT
technique, one or more optical properties of the
45 sample are monitored, and the point where the
value A changes radically is taken as "the clotting
end point" and the time interval from when the
coagulating agent is added to when clotting ends
is taken as APTT. PTT is substantially the same as
50 APTT.
The curve for the monitored value of A in
respect of one or more optical properties of the
plasma sample when a coagulating reagent has
been added, changes gradually in the initial stage,
55 changes more rapidly as clotting proceeds, and
then finally converges to a certain value.
The difference between the value of A prior to
coagulation and after the completion of
coagulation varies and depends on the sample. In
60 the case of absorbance, it is approximately
0.01—0.1 (Abs). Blood clotting time is taken by
measuring the time from when the coagulating
agent is added to when the optical properties of

the sample change. Conventionally, two methods
65 are used in detecting the point where the optical
properties change or when clotting is completed.
The first method is to differentiate the curve A
with respect to time and to detect when this
differential

$$\frac{dA}{dt}$$

exceeds a certain predetermined threshold value,
this moment being taken as the clotting end point.
In this method, when the setting of the threshold
value is changed relative to the chronological
75 change in the value of A during clotting, then the
moment detected as the clotting end point will
also change. Accordingly, if the amplitude of the
first differential of curve A changes, the clotting
end point also changes. For this reason, threshold
80 values have been set impirically in the prior art. In
order to avoid the empirical factors considered
undesirable for measuring the clotting time, the
following method has been used.
The second method takes as the clotting end
85 point not a predetermined gradient of curve A but
the steepest part of this curve A. In other words,
curve A is differentiated twice to obtain the
second differential

$$\frac{d^2A}{dt^2}$$

90 curve with respect to time. The point where the
amplitude of this curve crosses zero from the
positive side to the negative side is taken as the
clotting end point. In this case, the clotting end
point is determined by the optical properties of the
95 sample along because no threshold value is used
and therefore no influence is exerted by the level
at which threshold values are chosen. This second
method, therefore, is advantageous in that no
empirical factors enter in determining the clotting
100 end point.
As has been explained above, the first and the
second methods are useful for plasmas showing
normal clotting time characteristics. Generally,
blood coagulation tests should measure not only
105 the clotting time but should also adjust the said
clotting time with the activation curve or the
relation of clotting time and coagulation factor
concentration. In this case, the activating curve
presents the relation between coagulation factor
110 concentrations, or the concentrations of normal
pooled plasma in the solution of normal plasma
diluted with PSS (physiological saline solution),
fiblinogen or adsorped plasma. When normal
pooled plasma is diluted 10 times with PSS to seek
115 the above activating curve, the difference
between the value A taken prior to clotting and
after sufficient clotting decreases to about 1/10th
of that of the normal plasma. Clotting takes place
partially and not uniformly through the sample,
120 and the value A changes intermittently and not

uniformly with time, then converging to a certain value. The abnormal plasma which has a longer clotting time also presents the same tendency.

Thus, the curve A for the above samples
5 includes an additional wave component as if a higher frequency noise has been superimposed upon it. When clotting time in respect of such samples was measured by the first method mentioned above, the noise factor emphasized by
10 differentiation caused the first differential curve

$$\frac{dA}{dt}$$

to exceed the threshold value several times so as to generate several signals representing false end points, thus making it difficult to judge the true
15 end point.

As has been said, the advantage of the second method is that the clotting end point may be determined only by the optical properties of the sample. However, when the curve A includes a
20 noise factor accompanying the coagulation process, the noise factor is differentiated twice and generates numerous zero crossings of the second differential from positive to negative, making it more difficult than in the first method to
25 determine correctly the clotting end point. This is because its sensitivity toward the high frequency factor of noise is higher in the second differentiation than in the first differentiation.

In the prior art, the low pass filter has been used
30 in an effort to eliminate noise, but the results have not been sufficiently satisfactory.

In one example normal plasma was diluted 10 times with PSS and APTT was checked. After the coagulant agent was added to the plasma, the
35 value A measured in respect of optical properties of the sample gradually decreased with the time contrary to the case of normal plasma, slightly increased near the coagulation end point, and thereafter converged to a certain value.
40 In this test the second differential curve

$$\frac{d^2A}{dt^2}$$

crossed the zero from positive to negative not just once at the true end point but many times.

Thus, when the second method mentioned
45 above is used in testing such a sample, lots of signals are generated representing false end points besides the one for the true end point and cause a great deal of errors.

The present invention was contrived in view of
50 the defects of the conventional methods of measuring the blood clotting time as have been described above, and aims at offering an improved measurement of blood clotting time.

The present invention consists in a blood
55 clotting end point detector which includes means for monitoring an electrical signal representing the value of A of one or more optical properties of a blood plasma sample to which a coagulating agent has been added, means for deriving the first
60 and the second differentials with respect to time of the value A, means for detecting the moment Ta when the second differential changes from negative to positive or becomes positive, means for detecting the moment Tb when the second
65 differential next changes from positive to negative, means for deriving the difference (R) between the tangent to the curve A at the moment Ta and the curve A, means for determining whether the difference (R) or the integral, with
70 respect to time from moment Ta to moment Tb, of the different (R) exceeds a predetermined threshold value, in which case moment Tb is taken as the true clotting end point.

The invention further consists in a method of
75 detecting the blood clotting end point of a blood plasma sample to which a coagulating agent has been added, which includes monitoring an electrical signal representing the value A of one or more optical properties of the sample, deriving
80 the first and second differentials with respect to time of the value A, detecting the moment Ta when the second differential changes from negative to positive or becomes positive, detecting the moment Tb when the second
85 differential next changes from positive to negative, and identifying the moment Tb as the true clotting end point only if at least one of the following two conditions are satisfied:—

(i) the difference (R) between the tangent to the
90 curve A at moment Ta and the curve A exceeds a first predetermined threshold value,

(ii) the integral, with respect to time from the moment Ta to the moment Tb, of the said difference (R) exceeds a second predetermined
95 threshold value.

In the accompanying drawings:—

Figure 1 shows one form of apparatus which may be used for carrying out the present invention;
100 Figures 2 and 3 show typical examples of the curve A together with related curves, with and without noise respectively;

Figure 4 shows diagrammatically one embodiment for carrying out the present
105 invention;

Figure 5 shows a key-clamp type gate amplifier which may be used in the arrangement of Figure 4;

Figures 6 and 7 show diagrammatically two
110 alternative embodiments for carrying out the present invention; and

Figure 8 shows a hold amplifier which may be used in the arrangement of Figure 7.

In the accompanying drawings, Figure 1 shows
115 one form of apparatus which may be used for carrying out the present invention. A plasma sample (when using PT) or a plasma sample and Platelin-plus-activator (when using APTT) is placed in a sample cell 1. A controller 8 is then
120 activated to start the test causing a pump driver 9 to operate a pump 10 to pump a predetermined quantity of coagulation reagent from a supply 2

into the cell 1. Simultaneously timer 3 is started. Light from source 4 is directed onto cell 1 and light scattered by the sample is received by a photoelectric transducer 5 whose output is
5 amplified by amplifier 6 and fed to a coagulation end point detector 7 which in due course detects the end point and stops the timer 3. The timer thus records the clotting time.

Figures 2 and 3 show curves related to the
10 measurement of blood clotting time respectively in the case where a noise component is not included and where it is. Figure 2 shows an example of PT measurement where coagulating agent has been added to normal plasma and
15 Figure 3 shows an example of APTT measurement where normal plasma has been diluted 10 times with PSS.

In Figures 2 and 3 time t is plotted on the abscissa and Figures 2b and 3b show the
20 measured values A of one or more optical properties of the sample such as (1) absorbence, (2) transmittance of optical attention, (3) intensity of light scattered or its logarithmic value, (4) refractive index, (5) sum or difference of the
25 above (1) to (4). Figures 2c and 3c show the first differentials with respect to time.

$$\frac{dA}{dt}$$

of curves A, and Figures 2d and 3d their second differentials

30
$$\frac{d^2A}{dt^2}.$$

Figures 2a and 3a represent the areas indicated by the shading in Figures 2b and 3b, being the double integrals with respect to time of the first differentials shown in Figures 2c and 3c.
35 When coagulant agent is added to plasma when time $t=T_0$, the curve A takes the forms as shown in Figures 2b and 3b, the first differentials being shown in Figures 2c and 3c, and the second differentials in Figures 2d and 3d.
40 The moment when the second differential curve becomes positive or crosses the zero from negative to positive is set as Ta, and the moment when it crosses zero from positive to negative is set as Tb. Thus, Tb represents the steepest point
45 of the curve A. The second differential

$$\frac{d^2A}{dt^2}$$

is positive between the time Ta and Tb, and this becomes one of the requirements for detecting the clotting end point in this example.
50 The value of the first differential

$$\frac{dA}{dt}$$

at time $t=Ta$ is recorded and the difference between this and the value Co of A at the same moment, i.e.

55
$$(\frac{dA}{dt} - Co)$$

is twice integrated with respect to time t from Ta to Tb to obtain the curves in Figures 2a and 3a whose ordinates S is given as

$$S = \int_{Ta}^{Tb} \int_{Ta}^{Tb} (\frac{dA}{dt} - Co)\, dt\, dt$$

60 In other words, S is the twice integrated value of the difference (R) between the tangent to the curve A and A at time Ta, integrated with respect to time t from Ta to Tb, or the area between the respective times indicated by the oblique lines in
65 Figures 2b and 3b. The moment when this double integral S exceeds a predetermined threshold value C_1 is noted as Tc_1, and one of the requirements for detecting the clotting end point is that double integral S be bigger than C_1.
70 In order to judge whether the slope at Tb in the curve A meets one of the requirements for detecting the clotting end point in the present embodiment, the time when the first differential curve

75
$$\frac{dA}{dt}$$

exceeds a predetermined threshold value C_2 is noted as Tc_2; the other of the requirements for detecting the clotting end point is that the first differential value be greater than C_2.
80 When at least one of the above two requirements for detecting the end point in the present example are satisfied, then ensuing Tb is taken as the end point. In the above method, (1) the time when the value of the second differential

85
$$\frac{d^2A}{dt^2}$$

becomes positive from negative or from zero is set as Ta, and then the time it becomes negative from positive is set as Tb. In other words, the second differential

90
$$\frac{d^2A}{dt^2}$$

becomes positive between Ta and Tb; (2) the area S covered by the shading in Figures 2b and 3b is bigger than C_1 at $t=Tb$; (3) the slope of curve A in Figures 2b and 3b or

95
$$\frac{dA}{dt}$$

in Figures 2c and 3c is bigger than C_2 at time Tb;

(4) moment Tb at the steepest point of curve A is taken as the clotting end point.

This technique facilitates the reliable detection of the steepest portion of the curve A as the
5 clotting end point without interference from noises generated during the coagulation process. A detailed description will now be given of a device for putting this method into practice, referring to Figures 4 and 5. In Figure 4 IN
10 indicates input terminals, a, b, c, d voltage curves corresponding to Figures 2a, 2b, 2c, 2d, or 3a, 3b, 3c and 3d. Dif. 1 is the first differentiator, Dif. 2 the second differentiator, CMP. 0 the comparative unit to detect positive-negative
15 voltage wave d of the second differentiation, its output S_0 becoming logical 1 when the comparative unit input becomes positive. CGA is an amplifier to clamp and gate the voltage wave c of the first differentiation, the details of which are
20 shown in Figure 5.

INT. 1 is the first integrator, INT. 2 the second integrator, CMP. 1 a comparative unit, CMP. 2 a comparative unit, AND a logical "AND" circuit, MM the monostable multi-
25 vibrator to generate detection pulses for the clotting end point when logical product of S_0, S_1, S_2 changes to 0 from 1, OUT the output terminals, 0 reference voltage indicating zero voltage, C_1, C_2 reference voltages of predetermined values.
30 Values A measured in respect of optical properties of the sample as shown in Figures 2b and 3b are applied as the signal b on the terminal IN on the left side of Figure 4 and the once differentiated value

35
$$\frac{dA}{dt}$$

of the signal c is obtained by the differentiator Dif. 1, its curve being shown in Figures 2c and 3c. The signal c is again differentiated by the differentiator Dif. 2 to obtain second differential

40
$$\frac{d^2A}{dt^2}$$

or the signal d, its waves being shown in Figures 2d and 3d. The signal d is compared with OV by the comparing unit CMP. 0 and the output signal S_0 from the comparative unit CMP. 0 becomes
45 logical value 1 when the signal d or the second differential

$$\frac{d^2A}{dt^2}$$

is positive.
The first differential

50
$$\frac{dA}{dt}$$

from output of the differentiator Dif. 1, or c is applied to key-clamp type gate amplifier CGA. One example of such an amplifier is shown in Figure 5 wherein A_1 and A_2 denote buffer
55 amplifiers, output impedance of A_1 being extremely low and the input impedance of A_2 extremely high. Switch SW is for the clamp and the gate. When the logical value of the limit input LIN of Switch SW is zero, the input signal IN is
60 not transmitted to ouptut OUT, which is then 0. Output OUT in proportion to the changes in the input signal is obtained based on the input signal IN when the limit input LIN changes from the logical value 0 to 1. When the signal S_0 which
65 changes the logical value to 1 when the second differential

$$\frac{d^2A}{dt^2}$$

is positive is added to the limit input LIN of the switch SW to make logical value 1, the output
70 OUT is clamped to be OV against C_0, the first differential signal

$$\frac{dA}{dt}$$

applied to the input terminal.
Output OUT becomes proportional to the
75 difference between the first differential signal

$$\frac{dA}{dt}$$

applied to the input terminal and C_0. When S_0 becomes the logical value 0, then the output OUT again becomes 0. In Figure 4, the output from the
80 key-clamp type gate amplifier is applied to the integrator INT. 1. The aforementioned S_0 is applied to the re-set input terminal of the integrator INT. 1. accordingly, at the output of the integrator INT. 1 is obtained

85
$$\frac{dA}{dt} - C_0$$

integrated with respect to time or the change of the first differentiation from Ta when logical value of S_0 becomes 1 from 0. Thus, this output equals the difference (R) between tangent of A—t
90 curve at Ta and A.

The output at the integrator INT. 1 is applied to the input of the integrator INT. 2, and integrated as for the integrator INT. 1 and the output from the integrator INT. 2 becomes proportional to the
95 area covered by oblique lines in Figures 2b and 3b, or to the values of 2a and 3a. The output a from the integrator INT. 2 is applied to the input of the comparative unit CMP. 1 and compared with the predetermined threshold value C_1, and

bigger than C_1, then the output S_1 of the comparative unit 1 becomes the logical value 1. Whether or not the area of Figure 2a exceeds the predetermined threshold value C_1 is determined
5   by the above. Then

$$\frac{dA}{dt}$$

is applied to the comparative unit CMP. 2 and compared with the predetermined value C_2. If

$$\frac{dA}{dt}$$

10   is bigger than C_2, then the output S_2 of the comparative unit becomes the logical value 1. This will detect the slope in Figures 2b and 3b.
     Output S_0, S_1 and S_2 from respective comparative unit CMP. 0, CMP. 1 and CMP. 2
15   are applied to the input of the AND circuit, the output of which will give their logical product. When the logical value for these output signals is 1, three requirements for detecting the clotting end point are met, and it suffices merely to seek
20   the time when the output signal from the AND circuit becomes 0 from logical value 1, or when the logical product of S_0, S_1 and S_2 becomes 0 from 1 to seek the steepest portion of the curve A—t. Accordingly, the positive logical output
25   from the AND circuit is added to the input of monostable multivibrator which is triggered when the logical value changes from 1 to 0, the said vibrator giving a signal for the clotting end point.
     In the above example, two integrators INT. 1
30   and INT. 2 are used to perform integration of first differential

$$\frac{dA}{dt}$$

twice to seek the area. This can be performed by one integration. That is, the difference (R) of the
35   .tangent of the curve A—t at Ta and A may be compared directly with C_1. The requirement that the twice differentiated value

$$\frac{d^2A}{dt^2}$$

should be positive between Ta and Tb is not
40   necessarily needed if the time required for resetting the integrators INT. 1 and INT. 2 are not so long and the response from the comparative unit, CMP. 1, not so delayed. Accordingly, S_0 may be eliminated from the input of the AND circuit.
45   Although S_2 is used to determine the slope at Tb in the curve A—t, it is possible to eliminate it from the AND circuit input depending on the sample. The above explanation made in respect of an analog circuit is also valid in respect of a digital
50   circuit.

     Difference (R) between the tangent of the curve A—t and A at Ta, or S obtained by integrating the difference (R) with respect to time t from Ta to Tb can be sought by ways other than
55   that mentioned above. One of such ways is to seek the said difference (R) by double integrating the second differential curve

$$\frac{d^2A}{dt^2}$$

from Ta to Tb or to seek S by triple integration.
60   Figure 6 shows an example embodying this method. Except for the circuit structure, the example of Figure 6 functions identically as that of Figure 4 when the portion between IN—OUT is regarded as black box. In the method shown in
65   Figure 6, third integrator INT. 3, is provided in place of key-clamp type gate amplifier CGA of Figure 4, the input of which is connected to the output d of the second differentiator, Dif. 2, while the reset input of the third integrator, INT. 3,
70   is connected to the output S_0 of the comparative unit, CMP. 0. The rest are the same as those in Figure 4. That is, the second differential curve is used as the input for the third integrator INT. 3 in Figure 6 instead of the first differential curve c
75   used as the input for CGA whereas the output from the third integrator INT. 3 becomes the integrated value of the second differential curve integrated with respect to time from Ta to Tb, or

$$(\frac{dA}{dt} - Co)$$

80   in the method of Figure 4, equal to CGA output in Figure 4. The rest of operations in Figure 6 is identical to that in Figure 4.
     Another method is to integrate the once differentiated value

85   $$[\frac{dA}{dt}] = Co$$

at Ta with respect to time from Ta to Tb, its integrated value—time t curve becoming tangent for the curve A—t at Ta, and obtain the difference (R) by seeking the difference between
90   A and the said integrated value, or obtain S by integrating (R) with respect to time from Ta to Tb. Figure 7 shows an example of this method wherein functions are identical to those of Figure 4 when the portion between IN and OUT is
95   regarded as black box except for the circuit structure. The example in Figure 7 uses hold amplifier HA, fourth integrator INT. 4 and differential amplifier D-AMP instead of key-clamp type gate amplifier, CGA, and the first
100 integrator INT. 1. Input of hold amplifier HA is connected to the output c of the first differentiator Dif. 1, while limited input LIN of

hold amplifier HA is connected similarly to
output S_0 of the comparative unit CMP. 0.
    One embodiment of the hold amplifier is shown
in Figure 8 wherein A_1 and A_2 are buffer
5 amplifiers; output impedance of A_1 being
extremely low while input impedance of A_2
extremely high.
    When logical value of limit input LIN of switch.
SW, which is for holding, is 0, input signal IN is
10 transmitted to output OUT and the output is
proportional to the input. When limit input LIN
changes from logical value 0 to 1, the output OUT
maintains the value which is proportional to the
input signal at that moment unchanged by the
15 condenser C until the limit input LIN becomes 0
again. When the signal S_0 is applied to the limit
input LIN of switch SW to change the logical
value to 1 when the said twice differentiated value

$$\frac{d^2A}{dt^2}$$

20 is positive , and S_0 becomes the logical value 1
from 0 at time Ta, then the output from the hold
amplifier maintains the value proportional to the
on differentiated value

$$\left[\frac{dA}{dt}\right]=Co$$

25 applied to the input terminal at Ta until the time
Tb.
    Input of the fourth integrator, INT. 4, is
connected to the output of the said hold amplifier
HA while reset input of the fourth integrator INT.
30 4 is connected to the output S_0 of the comparative
unit CMP. 0. Accordingly, output from the fourth
integrator INT. 4 becomes the integral value of
the above C_0 integrated with respect to time from
Ta to Tb. This integral value—time t curve is
35 equivalent to the tangent of the curve A—t at TA.
    Input on the sample side of differential
amplifier D-AMP is connected to IN terminal b
on which the measured value A is applied whereas
the input on reference side is connected to the
40 output of the above mentioned fourth integrator
INT. 4, and the difference between these two
signals or the difference (R) between the tangent
of the curve A—t and A at Ta is obtained as
output. Accordingly, the output from the
45 differential amplifier D-AMP is the same as
output of the first integrator INT. 1. The rest of
operations in the system of Figure 7 are identical
to those of Figure 4.
    Although the above description was made in
50 respect of the analog circuit, the same effects are
achieved by using a digital circuit when the digital
measured value A signals converted by analog-to-
digital converter are used.
    As has been explained, the present invention
55 offers excellent operational effects in securely
performing the blood clotting time measurement
such as PT, APTT and PTT by stably detecting as

the clotting end point the steepest portion of the
curve A, values measured of optical properties of
60 the sample, —time t, free of noise effects. In
Figure 3a there can be seen two small pulses
between moment To and moment Ta which
represent integrated noises which have been
rejected by the system thereby avoiding false end
65 points.
    The present method exerts similar effects in
detecting the clotting end point when measuring
the clotting time for platelet as for the blood
clotting time.

70 CLAIMS
    1. A blood clotting end point detector which
includes means for monitoring an electrical signal
representing the value A of one or more optical
properties of a blood plasma sample to which a
75 coagulating agent has been added, means for
deriving the first and the second differentials with
respect to time of the value A, means for
detecting the moment Ta when the second
differential changes from negative to positive or
80 becomes positive, means for detecting the
moment Tb when the second differential next
changes from positive to negative, means for
deriving the difference (R) between the tangent to
the curve A at the moment Ta and the curve A,
85 means for determining whether the difference (R)
or the integral, with respect to time from
moment Ta to moment Tb, of the difference (R)
exceeds a predetermined threshold value, in
which case moment Tb is taken as the true
90 clotting end point.
    2. A detector as claimed in Claim 1, wherein the
means for deriving the difference (R) includes
means for deriving the difference between the
first differential and the value of the first
95 differential at moment Ta.
    3. A detector as claimed in Claim 2, which
includes means for twice integrating the
difference (R) with respect to time from the
moment Ta to the moment Tb, the moment Tb
100 being taken as the true end point provided the
twice integrated value exceeds a predetermined
threshold value.
    4. A detector as claimed in Claim 1, which
includes means for twice integrating the second
105 differential.
    5. A detector as claimed in Claim 1, which
includes means for detecting whether the value of
the second differential at moment Tb exceeds a
predetermined threshold value, the moment Tb
110 being taken as the true end point only if said value
is exceeded.
    6. In a device where the blood clotting time is
measured, displayed and recorded by starting an
electronic timer at the point when coagulating
115 agent is added to plasma solution in the
coagulation measuring sample cell, amplifying the
electric signals generated as the light from the
light source is applied to the photoelectric
transducer via the said sample cell, and by
120 stopping the said electronic timer by clotting end
point detection signals obtained by applying the

said analog amplified measured value A signals or digital measured value A signals which have been converted from the analog signal by an analog-to-digital converter, to either an analog or digital
5 clotting end point detector, a blood clotting end point detector comprising a first differentiator wherein the said measured value A signals are differentiated with respect to time, a second differentiator connected to the first differentiator
10 and wherein the signals are again differentiated, means for detecting the point where the second differential changes from negative to positive which is set as the first standard point Ta, and for detecting the point where the second differential
15 changes from positive to negative which is set as the second standard point Tb, means for deriving the difference (R) between the tangent of the curve of measured value A with time at the said first standard point Ta and the measured value A,
20 means for detecting when the said difference (R) exceeds a predetermined threshold value, or when the integrated value of the difference (R) with respect to time from the first standard point Ta to the second standard point Tb exceeds a

25 predetermined threshold value, in which case the second standard point Tb is taken as the true clotting end point.

7. A method of detecting the blood clotting end point of a blood plasma sample to which a
30 coagulating agent has been added, which includes monitoring an electrical signal representing the value A of one or more optical properties of the sample, deriving the first and second differentials with respect to time of the value A, detecting the
35 moment Ta when the second differential changes from negative to positive or becomes positive, detecting the moment Tb when the second differential next changes from positive to negative, and identifying the moment Tb as the
40 true clotting end point only if at least one of the following two conditions are satisfied:
(i) the difference (R) between the tangent to the curve A at moment Ta and the curve A exceeds a first predetermined threshold value;
45 (ii) the integral with respect to time from the moment Ta to the moment Tb, of the said difference (R) exceeds a second predetermined threshold value.